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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/707,117	WOLFF ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,7,11,12,16-20,24,25,28-31,34-36 and 38-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,11,12,16-20,24,25,28-31,34-36 and 38-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-30-04 has been entered.

Applicant's arguments filed 3-30-04 have been fully considered but they are not persuasive. Claims 5 and 27 are newly canceled. Overall, claims 4, 5, 8-10, 13-15, 21-23, 26, 27, 32, 33 and 37 have been canceled. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 38-42 remain pending and under consideration. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

In claim 35, delete "around the limb" to be more clear.

In claim 39, step a), insert "of the mammal" after "a blood vessel in a limb" to be more clear.

In claim 39, step a), make "applying pressure to the limb" a separate step. The step can be more clearly written as "applying pressure to the skin of the limb such that blood flow to the limb is impeded."

In claim 39, step b), insert "of the limb" after "skeletal muscle cells" to be more clear.

In claim 39, step c), insert "in the skeletal muscle cells" to be more clear.

Claim Rejections - 35 USC ' 112

1. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 38-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation of applying external pressure against the mammal's skin is found on pg 3, ¶ 2.

The rejection regarding continuous and transient immunosuppression (claim 1) has been withdrawn because the phrase has been deleted.

The rejection regarding the phrase "function is not affected by the delivery process" in claim 39 has been withdrawn because the phrase has been deleted.

The phrase "immunosuppressive treatment" in claim 1 is new matter.

The terms "superficialis" and "profundus" (12) are new matter. Pg 26 uses the abbreviations "prof." and "spf." The specification does not define the abbreviations and the literature at the time of filing does not support an art-recognized definition for "prof." and "spf." One of skill would not have known "prof." and "spf." meant profundus and superficialis.

The limitation of "applying a tourniquet around the limb" (34), "applying a cuff around the limb" (35) are new matter.

Impeding "blood flow to the limb" in claim 39, step a) is new matter. The specification discusses impeding blood flow in the blood vessel being injected; it does not discuss impeding "blood flow to the limb" on pg 5, lines 13-24, or anywhere else in the specification.

The phrase "distal to" in claim 39, step b) is new matter. Pg 32, line 19, refers to expression occurring distal to the tourniquet, which is not the same as delivering the polynucleotide to mammalian skeletal muscle cells distal to the applied pressure as claimed. Obtaining delivery and obtaining expression have different scopes because delivery can occur without expression.

The phrase "does not diminish the use of the limb by the mammal" in claim 39 is new matter. Pg 22, lines 15-27, discusses histological muscle damage caused by the method. Pg 25, lines 17-25, discusses monkeys having full function of their arms after the procedure. Pg 28, lines 6-23, discusses serum characteristics and histologic

analyses of monkeys after the procedure. None of the citations states the procedure "does not diminish the use of the limb by the mammal" as broadly claimed. The closest citation is pg 25, lines 17-25, however, pg 25, lines 17-25, is limited to a procedure that does not diminish the use of the limb by the mammal after the procedure.

The phrase "repetitive treatment" in claim 40 has support on pg 29, lines 1-2, which teaches administering dexamethasone and every day thereafter.

The phrase "a single treatment" in claim 41 is new matter.

Applicants are reminded that failure to cite support for new limitations is not an acceptable procedure and should result in a non-responsive letter. In an effort to expedite prosecution, the examiner has made new matter rejections. Please provide support for new limitations at the time the new limitations are added to the claims.

2. Claims 1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel, wherein said DNA comprises a nucleic acid sequence encoding a marker protein operably linked to a promoter and wherein said marker protein is expressed to detectable levels in muscle cells of said limb, does not reasonably provide enablement for expressing protein in skeletal muscle cells by occluding any limb, injecting any blood

vessel and delivering the DNA to any skeletal muscle cell as broadly claimed; injecting a viral vector into a blood vessel of a limb to obtain expression in skeletal muscle; or how to deliver DNA to a blood vessel of one limb and expressing the DNA in skeletal muscle of another limb. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 1 encompasses delivering a polynucleotide to any limb skeletal muscle cells so that expression occurs in any cell to detectable levels. Claim 1 encompasses delivering a polynucleotide to any limb skeletal muscle by injecting/occluding any blood vessel.

Claim 3 requires injecting a viral vector into a blood vessel of a limb to obtain delivery to a skeletal muscle cell.

Claims 6-26 and 28-31 require delivery to skeletal muscle cells of limbs, some of which require delivery to specific muscles within the limbs.

Claim 39 encompasses delivering a polynucleotide to any mammalian skeletal muscle cells so that expression occurs in any cell to detectable levels. Claim 39 encompasses delivering a polynucleotide to any mammalian skeletal muscle distal to the applied pressure.

Vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art (Miller of record,

1995, FASEB J., Vol. 9, pages 190-199; Deonarain of record, 1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, first paragraph; pg 65, first para. under Conclusion section; Verma of record, Sept. 1997, Nature, Vol. 389, pages 239-242; see entire article; pg 240, sentence bridging col. 2 and 3; Crystal of record, 1995, Science, Vol. 270, pg 404-410; pg 409).

The specification teaches administering naked plasmid DNA encoding a marker protein operably linked to a promoter to an artery of the arm or leg and obtaining expression in muscle cells of the arm or leg, respectively. However, Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) taught administering adenoviral particles to a femoral artery and vein occluded using a tourniquet did not result in expression in the muscle surrounding the perfused limb (but did result in expression in hepatocytes) (page 2201, col. 2, 2nd and 3rd ¶.). Ye (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627) taught administering adenoviral particles encoding LacZ to the portal vein/artery occluded with clamps and obtaining expression in kidney, liver and spleen but not in skeletal muscle or heart.

The specification does not teach delivering DNA to a blood vessel of one limb and expressing the DNA in skeletal muscle of another limb as broadly encompassed by claims 1 and 39. For example, the specification does not teach delivering DNA to a blood vessel in the leg and obtaining expression in muscle cells of the arm. Given the unpredictability in the art taken with the lack of guidance provided in the specification, it

would have required one of skill in the art at the time the invention was made undue experimentation to determine the parameters required to deliver DNA to skeletal muscle as claimed, particular to express the DNA in skeletal muscle.

The specification does not teach how to use a viral vector injected into a blood vessel of a limb to obtain expression in skeletal muscle (claim 3) because Ye did not obtain expression in muscle cells by injecting adenovirus into an occluded blood vessel of a limb and because the specification does not teach how to overcome the teachings of Ye.

The broad claims encompass delivery to any skeletal muscle and narrower embodiments require delivery to specific muscles of the arm and leg (claims 11, 12, 16, 17, 24, 25, 29-31). It cannot be determined how the delivery of DNA to specific muscles of the arm and leg is effected by the location of the blood vessel injected, the type of polynucleotide (adenovirus vs. naked plasmid DNA), the method of occlusion (tourniquet vs. clamps, balloon catheter), or the method of immunosuppressing (administering vs. not administering an immunosuppressive agent) as broadly claimed. Applicants have not taught how much pressure is required to obtain expression in the specific skeletal muscles of the arm and leg. While the specification teaches expressing proteins in specific muscles of the arm and leg using naked plasmid DNA, the claims are not limited to naked plasmid DNA, and the specification does not correlate the results obtained with naked plasmid DNA to any other vector (e.g. adenovirus).

The specification does not provide adequate guidance for one of skill to determine why or when an immunosuppressive agent is administered, when an immunosuppressive agent is required to obtain expression in the desired skeletal muscle cell, how administering such an agent effects the delivery of DNA or whether different immunosuppressive agents have different effects on the delivery of DNA. Clarification is required.

The specification does not enable delivering any polynucleotide as broadly claimed. The specification only teaches delivering DNA encoding a marker protein operably linked to a promoter. The specification does not enable delivering any other polynucleotide or delivering DNA encoding a marker protein in the absence of a promoter.

Applicants' arguments regarding the distinctions between Milas and applicants invention are misplaced under enablement (pg 8 of response filed 3-3-04, 2nd full ¶). Applicants have not provided any reason why Milas enables applicants' invention as broadly claimed.

Applicants argue "claims 11, 12, 17, 24, 25 and 29-31 are not "restricting delivery to the explicitly named muscle cells. The named muscle cells are present in the arm or leg and therefore practice of the invention results in the delivery to the claimed muscle cells." These two sentences are in direct opposition to each other. Delivery to the explicitly named muscle cells is required in the claims and the parameters required to

obtain delivery to those specific muscle cells is not adequately described in the specification for reasons of record. For example, mere delivery to the arm does not necessarily result in delivery to the muscles of the hand as in claims 18-20. Applicants have not described how close one must inject the DNA to the hand to obtain delivery in the hand or described how to inject the DNA at the top of the arm and obtain delivery in the hand.

Applicants' cite pg 32, Example 10, and state injection into the popliteal artery with occlusion proximal to the injection results in delivery of the polynucleotide to muscle cells in the lower leg but not the thigh (pg 8, 5th full ¶ of response filed 3-30-04). Applicants' argument is not persuasive. Example 10 shows obtaining expression in the quadriceps, biceps femoris, hamstrings, gastrocnemius, lower shin muscles and muscles of the plantar surface. Example 10 does not show obtaining delivery to a "soleus muscle cell" (claim 24), a popliteus muscle cell, flexor digitorum longus muscle cell, flexor halluci longus muscle cell or tibialis posterior muscle cell (claim 25), a tibialis anterior muscle cell, an extensor hallucis longus muscle cell, extensor digitorum longus muscle cell, or abductor hallucis longus muscle cell (claim 29), a peronaus longus muscle cell, peronaus brevis muscle cell (claim 30), an extensor digitorum brevis muscle cell or an extensor hallucius brevis muscle cell (claim 31) by injecting the popliteal artery with occlusion. Example 10 does not show delivery of the polynucleotide to the minor muscles of the leg or foot as claimed.

Applicants argue examples using similar processes demonstrate delivery of DNA/polycation complexes, small double stranded RNA oligonucleotides and viral particles were provided previously, thus enabling injecting any polynucleotide as broadly claimed. The data can be found in the declaration filed 5-9-03 but is not persuasive. The method of delivering adenovirus required administering papaverine and collagenase pre-injection, which is not taught in the specification. $5x10^8$ adenoviral particles/10 ml saline was injected within 10 seconds, which is not taught in the specification. In addition, the claims are not limited to delivering adenovirus, or to delivering adenovirus in combination with papaverine and collagenase before injection, or to injecting the adenovirus within 10 seconds. Therefore, the data in the specification does not correlate to the teachings in the specification and is not persuasive because it provides more teachings than were provided in the specification that were essential to deliver adenovirus to skeletal muscle cells as claimed. Therefore, the limitation of "viral vector" in claim 3 remains rejected for reasons of record.

Applicants argue that the claims do not have to result in expression of a protein in the skeletal muscle cells (pg 9, 3rd and 4th ¶ of response filed 3-30-04). Applicants point to antisense technology. Applicants' arguments are not logical and do not correlate to the claim language. Claims 1 and 39 require expression of the polynucleotide at detectable levels, which excludes antisense technology. The expression must occur in the skeletal muscle cells in which the polynucleotide has been

delivered as claimed. The polynucleotide must encode a protein operably linked to a promoter for expression to occur. Please amend the claims accordingly.

3. Claims 1-3, 5-7, 11, 12, 16-20, 24, 25, 27-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The previous rejections regarding claim 1 have been withdrawn in view of the amendments to the claims.

Claim 1 is newly indefinite for the following reasons:

The phrase "of the limb" (claim 1, step a) lacks antecedent basis. The preamble refers to "a limb skeletal muscle cell," not a limb. The phrase "inserting the polynucleotide in a solution into a blood vessel in a limb of the mammal" would overcome this rejection.

The phrase "the mammal's skin" does not properly correlate to the limb of step a) of claim 1. As written, it appears that the claim encompasses exerting pressure anywhere on the mammal's skin to impede blood flow in the blood vessel. However, the pressure must be exerted to the skin of the limb being injected. Therefore, the step should be limited to "applying external pressure against the skin of the limb such that blood flow through the blood vessel is impeded."

The metes and bounds of claim 1 steps b) and c) are indefinite. It is unclear if administering immunosuppressive treatment (c) may be the result of the applying pressure to the skin in step (b) or if administering immunosuppressive treatment must be a new, separate step. Applying a tourniquet, for example, may be an "immunosuppressive treatment" because it inhibits cells of immune from flowing into the limb. Therefore, it is unclear if applying a tourniquet meets the limitations of steps b) and c), or if a second, separate immunosuppressive treatment must be administered.

The phrase "wherein delivery of the polynucleotide to the limb skeletal muscle cells results in expression" in claim 1 lacks antecedent basis and does not clearly set forth that delivery of the polynucleotide to the limb skeletal muscle occurs. It cannot be determined if the phrase is an intended use or if delivery of the polynucleotide to the limb skeletal muscle must occur. The phrase "such that the polynucleotide is delivered to the limb skeletal muscle cells and expressed in the limb skeletal muscle cells to detectable levels" would overcome this rejection.

In claim 1, "delivery of the polynucleotide to the limb skeletal muscle cell" does not have the same scope as "results in expression of the polynucleotide at detectable levels". It is unclear if the expression is limited to limb skeletal muscle cell after delivery to limb skeletal muscle cells or if expression may occur anywhere after delivery to limb skeletal muscle cells.

The rejection regarding skeletal muscle cell vs. muscle cell in claim 5, 6, 18, 19, 20, 24, 28 and 30 is withdrawn because claim 5 was canceled and claims 6, 18, 19, 20, 24, 28 and 30 now use parallel language.

The dependency of claims 11, 12, 16, 17, 34 and 35 has been fixed.

Claims 34 and 35 are indefinite because "applying pressures" does not have proper antecedent basis. The claims must refer to "applying external pressure" (emphasis added) as in claim 1.

The rejection of claims 11, 12, 16, 17, 30 and 31 regarding species in the Markush group being types of muscles, not muscle cells as claimed has been withdrawn in view of the amendments.

The rejection regarding internal muscle cell in claims 27 and 30 has been withdrawn because claim 27 was canceled and claim 30 was amended.

The rejection regarding spf and prof (claims 11 and 12) has been withdrawn because the terms have been replaced with superficialis and profundus.

The rejection regarding compressing skin (34-36) has been withdrawn because the phrase has been changed to "applying pressure against the mammal's skin".

The rejection of claims 34-36 regarding whether a tourniquet or cuff is applied over the skin has been withdrawn in view of the amendment.

The rejection regarding "cuff" (claims 35, 36) has been withdrawn. While the specification defines "cuff" as "a devise for impeding blood flow through mammalian

internal blood vessels," the specification states, "for purposes of the claims, cuff refers specifically to a device applied exterior to the mammal's skin and touches the skin in a non-invasive manner (page 5, lines 13-15). Therefore, the term "cuff" is limited to a device for impeding blood flow that is applied exterior to the mammal's skin and touches the skin in a non-invasive manner.

The rejection regarding "primarily" (claim 37) has been withdrawn because the claim has been canceled.

The rejection regarding the metes and bounds of non-vascular parenchymal cells (claim 38) has been withdrawn in view of applicants' arguments.

Claim 38 is newly rejected because delivery to "non-vascular parenchymal cells" does not further limit delivery to the "limb skeletal muscle cell" as in parent claim 1.

The previous rejections regarding claim 39 have been withdrawn in view of the amendments to the claims.

Specifically, the rejection of claim 39 regarding the metes and bounds of "full function" has been withdrawn because the term "full" was deleted in the response filed 7-12-02.

The rejection of claim 39 regarding the metes and bounds of "wherein function is not affected by the delivery process" has been withdrawn because the phrase has been deleted.

Claim 39 is newly rejected as follows:

The steps of claim 39 do not use parallel language.

For example, step a) encompasses inserting a polynucleotide into a blood vessel in any limb, but the preamble is limited to delivering a polynucleotide to a skeletal muscle cell in a mammal. It is unclear if step a) should be limited to the limb of a mammal or whether it encompassed delivery to the limb of an animal.

Impeding "blood flow to the limb" as in claim 39, step a) does not make sense in view of the specification. The blood flow at the site of injection in the blood vessel is impeded. The specification does not discuss impeding "blood flow to the limb" on pg 5, lines 13-24, or anywhere else in the specification.

Step b) of claim 39 does not parallel the language in step a) or the preamble by stating the polynucleotide is delivered to skeletal muscle cells in the limb or of the mammal.

The phrase "distal to" in claim 39, step b) is unclear. Which direction is "distal" to the applied pressure?

In claim 39, "delivering the polynucleotide to mammalian skeletal muscle cells" (step b) does not have the same scope as "expressing the polynucleotide to detectable levels" (step c). It is unclear if the expression is limited to mammalian skeletal muscle cells after delivery to mammalian skeletal muscle cells or if expression may occur anywhere after delivery to mammalian skeletal muscle cells.

In claim 39, the phrase "wherein inserting the polynucleotide, applying pressure, and expressing the polynucleotide does not diminish use of the limb by the mammal" is unclear. It is unclear if the phrase is intended to mean that the mammal can still use the limb after the steps occur or if the phrase means the limb can still be used during the method.

In claim 39, the metes and bounds of what applicants consider "diminished use of the limb" cannot be determined. It is unclear if the phrase is limited to diminished functional parameters of the limb or if the phrase encompasses the diminished frequency of use of the limb.

The rejection of claim 40 regarding the metes and bounds of "continuous" use has been withdrawn because the term has been deleted.

Claim 40 is newly rejected because "repetitive treatment" does not make sense. While treatments are repetitive, and one may receive "repetitive treatments", one "treatment" as claimed is not "repetitive".

The rejection of claim 41 regarding the metes and bounds of the term transient treatment has been withdrawn because the phrase has been deleted.

The rejection of claim 42 has been withdrawn in view of the amendment.

Claim Rejections - 35 USC ' 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 38-42 are newly rejected under 35 U.S.C. 102(e) as being anticipated by Draijer-van der Kaaden (US Patent 6,495,131).

Draijer-van der Kaaden taught administering adenovirus to the femoral vein using a tourniquet around the groin (detailed description, paragraph 25). Using a tourniquet is administering an immunosuppressive treatment as claimed. '131 has priority back to July 13, 1998.

6. Claims 1, 3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 38-41 remain rejected under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Milas taught administering adenoviral particles to an occluded femoral artery and vein of a rat. The femoral artery and vein were occluded using a tourniquet applied to the skin of the leg (pg 2198, Fig. 1A, see tourniquet on rat). The adenoviral vector encoded LacZ and was expressed in hepatocytes; hepatocytes are parenchymal cells. Applying a tourniquet is equivalent to "administering immunosuppressive treatment". The DNA of Milas was inherently delivered to skeletal muscle cells because occlusion of the femoral artery using a tourniquet results in delivery of the DNA to skeletal muscle and is the same method used by applicants in Example 10 (pg 32). Milas taught LacZ was expressed in tumor cells, which is equivalent to "expression at detectable levels" as claimed. The claims do not require expression in skeletal muscle cells. Claim 42 has been withdrawn because Milas did not teach "oral treatment" or "treatment by subcutaneous injection".

Applicants argue Milas did not teach delivery to muscles as claimed because pg 2201, 3rd full ¶, states no β–gal expression was apparent in the muscle tissue of the perfused limb. Applicants' argument is incomplete and not persuasive. Applicants have not address the claim language, which does not require expression in muscle tissue. Milas taught LacZ was expressed in tumor cells of the mammal, which is encompassed

by the phrase "results in expression of the polynucleotide at detectable levels." While Milas taught no expression of β-gal was detected in muscle cells of the perfused limb (pg 2201, 3rd full ¶), the claims do not require expression in muscle cells. DNA of Milas inherently was delivered "to the limb skeletal muscle cells" as claimed because the method of Milas is identical to the method on pg 32, Example 10, which described delivering DNA to muscle tissue. In addition, Milas taught the muscle tissue of perfused leg was different than normal because it had small inflammatory cell infiltrates (pg 2201, 3rd full ¶). Small inflammatory cell infiltrates are an indication that the DNA had inherently been delivered "to the limb skeletal muscle cells".

Applicants' arguments under enablement on pg 8, 2nd ¶ of the response filed 3-30-04 are misplaced but are addressed here. Passing the tourniquet "underneath the inguinal ligament" still requires that the tourniquet touch the skin of the leg in areas not in the surgical field. In addition, Milas first placed the tourniquet around the leg and secured it by a hemostat (which meets the limitation of the claim), and then the free end of the tourniquet was passed "underneath the inguinal ligament." Applicants' second and third points cannot be determined and does not distinguish the teachings of Milas from the claims. The claims are not limited to injecting a single blood vessel. The claims do not exclude ligating the vessel after the procedure.

7. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 102(a) as being anticipated by Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364) for reasons of record.

Von der Leyen taught administering naked plasmid DNA into the carotid artery while applying a sphygmomanometer to the skin of the limb to increase the pressure of the artery to 300 mmHg (pg 2356 col. 2, Transfection procedure; pg 2360, Fig. 2, see 300). Applying a sphygmomanometer is equivalent to "applying immunosuppressive treatment." While Von der Leyen did not explicitly teach obtaining delivery to skeletal muscle as claimed, Von der Leyen implicitly taught obtaining delivery to skeletal muscle. Von der Leyen obtained expression in the layers of the carotid artery; therefore, the method of Von der Leyen inherently results in delivery beyond the blood vessel wall and into skeletal muscle as claimed because the carotid artery is surrounded by skeletal muscle. Inherency is also relied upon because Von der Leyen forced the DNA through the blood vessel wall (pg 2362, col. 1, line 14) and because the method of administering taught by Von der Leyen is equivalent to the method taught by applicants in the specification.

Applicants argue Von der Leyen did not teach using the sphygmomanometer to increase the pressure in the artery. Applicants' argument is not persuasive. Blood pressure cuffs inherently increase the pressure in the artery by blocking off blood flow.

The reason why Von der Leyen used the sphygmomanometer is irrelevant because it caused an external pressure on the blood vessel as claimed.

Applicants' argument that Von der Leyen did not teach putting the sphygmomanometer around the limb is unfounded. Such a broad statement, without pointing to the teachings of Von der Leyen or a citation of Von der Leyen or without providing any reasoning, cannot be addressed.

Applicants argue that while Von der Leyen observed delivery to multiple layers of the artery, Von der Leyen did not observe delivery out of the vessel to skeletal muscle. Applicants' argument is not persuasive. Von der Leyen did not test for delivery in skeletal muscle. However, the method of Von der Leyen inherently results in expression in skeletal muscle cells because Von der Leyen forced DNA through the muscle wall (pg 2362, col. 1, line 14), resulting in expression at least throughout the artery itself. This method is equivalent to the method in the specification. Therefore, the method of Von der Leyen inherently results in delivery of DNA to skeletal muscle and expression in skeletal muscle cells.

Claim Rejections - 35 USC ' 103

8. Claims 1-3, 6, 11, 12, 16, 17, 28, 30, 31, 34 35, 36 and 38-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Budker (1998, Gene Therapy, Vol.

5, pg 272-276) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Budker taught administering naked plasmid DNA encoding marker protein into an artery in the leg of a rat, wherein pressure was applied to the artery using microvessel clips. Administration resulted in marker protein expression in all muscle groups of the leg (pg 274, col. 2, 1st full para.). The limitation of applying transient immunosuppression (claim 1, step c) is equivalent to temporarily occluding the blood vessels; the process of occluding blood vessels is immunosuppression because blood cells are prevented from flowing through that area. The limitation of applying continuous immunosuppression (claim 1, step c) is taught by Milas because occlusion continues throughout the operation. The metes and bounds of continuous and transient immunosuppression are unclear (see 112/2nd). Budker also taught injecting collagenase is also equivalent to applying immunosuppression because it disrupts the capillary membranes thereby decreasing the flow of blood through the immune system, which is equivalent to immunosuppression. Budker did not teach applying pressure to the mammal's limb skin as claimed.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an artery in the leg of a rat using pressure to deliver the DNA to all the muscle groups of the leg as taught by Budker wherein the plasmid was administered to the femoral artery and pressure was applied using a tourniquet applied to the epidermis of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using microvessel clips with using a tourniquet to reduce damage to the blood vessel and to eliminate time in surgery spent applying microvessel clips.

Applicants argue they have shown that Milas did not teach using a device over the skin. Applicants' argument cannot be found, but Milas taught the limb was shaved and a tourniquet was applied to the limb (pg 2192, col. 2, "Operative Technique: Isolated Limb Perfusion"). Therefore, a tourniquet on the skin provided external pressure.

9. Claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) in view of Nabel (US Patent 5,910,488, June 8, 1999) for reasons of record.

Milas taught adenoviral particles to a femoral artery of a rat that was occluded using a tourniquet applied to the skin of the leg (pg 2198, Fig. 1A, see tourniquet on rat). The adenovirus was inherently delivered to skeletal muscle cells as claimed because the method of Milas is identical to that used by applicants in Example 10 (pg 32). Milas taught LacZ was expressed in tumor cells, which is equivalent to "expression at detectable levels" as claimed. Milas did not teach using immunosuppression or naked DNA.

However, Nabel taught pre-treating with cytoxan (an immunosuppressant), and injecting naked plasmid DNA into an occluded blood vessel (col. 25, Example 14, lines 38-67; claim 20, col. 15, line 23). The limitation of applying immunosuppression is equivalent to pre-treating with cytoxan, which eliminated suppressive T-cells. The pre-treating with cytoxan is transient immunosuppression (claim 1, step c) because the T-cells may return and continuous immunosuppression (claim 1, step c) because the suppressive T-cells are eliminated throughout the operation.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer DNA into an artery using a tourniquet as taught by Milas wherein the artery was pre-treated using cytoxan as taught by Nabel. One of ordinary skill in the art at the time the invention was made would have been motivated to pre-treat the blood vessel of Milas with cytoxan to eliminate suppressive T-cells. One of ordinary skill in the art at the time the invention was made would have been

motivated to use the method of Nabel using the tourniquet of Milas to eliminate steps in surgery. One of ordinary skill in the art at the time the invention was made would have been motivated to use the method of Nabel to deliver DNA to muscle tissue to treat tumors in/adjacent to muscle tissue.

Applicants argue the "amended claims do not encompass the method taught by Milas for reasons stated in the § 112 rejections." Applicants' argument is lacking in any reasoning and does not specifically point to limitations that are not taught by the references taken together. Applicants have ignored the fact that the rejection is based on the combined teachings of Milas and Nabel. Milas taught the limb was shaved and a tourniquet was applied to the limb (pg 2192, col. 2, "Operative Technique: Isolated Limb Perfusion"). Therefore, a tourniquet on the skin provided external pressure.

10. Claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 38-42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (US Patent 6,265,387, July 24, 2001) in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Wolff taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the liver (col. 17, Example 8). Some of the animals received subcutaneous administration of dexamethasone the day before surgery (col. 18, line 45). The method of Wolff inherently resulted in delivery to skeletal muscle as claimed

because the method requires increased pressure in the blood vessel as a result of the clamps and the delivery of the DNA within a short amount of time. Wolff did not teach using a tourniquet.

However, Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an artery in the leg of a rat using pressure to deliver the DNA to all the muscle groups of the leg as taught by Wolff using a tourniquet applied to the epidermis of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps of Wolff with using the tourniquet of Milas to reduce damage to the blood vessel and to eliminate time in surgery spent applying microvessel clips. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Milas with the plasmid DNA of Wolff to prevent viral infection and to integrate the DNA into the genome.

Applicants argue the "amended claims do not encompass the method taught by Milas for reasons stated in the § 112 rejections." Applicants' argument is lacking in any reasoning and does not specifically point to limitations that are not taught by the

references taken together. Applicants have ignored the fact that the rejection is based on the combined teachings of Wolff and Milas. Milas taught the limb was shaved and a tourniquet was applied to the limb (pg 2192, col. 2, "Operative Technique: Isolated Limb Perfusion"). Therefore, a tourniquet on the skin provided external pressure.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states, "whoever invents or discovers any new and useful process ... may obtain a patent therefore..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-3, 6, 11, 12, 16, 17, 24, 25, 28-31, 34-36 and 38-42 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,265,387 in view of Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pages 2197-2203) for reasons of record.

Wolff claimed delivering naked plasmid DNA to a bile duct, increasing the permeability of the bile duct and obtaining delivery and expression in the liver. Wolff did not claim delivering DNA to skeletal muscle as claimed.

However, Wolff taught clamps applied to the femoral artery increased permeability of the artery and taught delivering naked plasmid DNA to a clamped femoral artery and obtaining expression in the liver (col. 17, Example 8). Some of the animals received subcutaneous administration of dexamethasone the day before surgery (col. 18, line 45). The method of Wolff inherently resulted in delivery to skeletal muscle as claimed because the method required increased pressure in the blood vessel as a result of the clamps and the delivery of the DNA within a short amount of time.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into a vessel, increasing permeability and obtaining expression as claimed by Wolff wherein the vessel was a femoral artery, the permeability was increased using clamps and the DNA was delivered to skeletal muscle as taught in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated

to inject the femoral artery instead of the bile duct as suggested in the specification of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to use clamps to increase permeability in light of the disclosure of Wolff. One of ordinary skill in the art at the time the invention was made would have been motivated to deliver DNA to skeletal muscle instead of the liver as suggested in the disclosure of Wolff. The combined teachings of the claim and disclosure of Wolff did not teach using a tourniquet.

Milas taught administering DNA to a femoral artery of a rat that was occluded using a tourniquet applied to the epidermis of the leg (pg 2198, Fig. 1A, see tourniquet on rat).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer naked plasmid DNA encoding marker protein into an artery in the leg of a rat using pressure to deliver the DNA to all the muscle groups of the leg as taught by the combined teachings of the claim and disclosure of Wolff using a tourniquet applied to the epidermis of the leg as taught by Milas. One of ordinary skill in the art at the time the invention was made would have been motivated to replace using clamps with using the tourniquet to reduce damage to the blood vessel and to eliminate time in surgery spent applying microvessel clips. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral

vector of Milas with naked plasmid DNA to prevent viral infection and to integrate the DNA into the genome.

Applicants argue Milas did not teach applying a tourniquet over the skin to impede blood flow. Applicants' argument is not persuasive. Milas taught the limb was shaved and a tourniquet was applied to the limb (pg 2192, col. 2, "Operative Technique: Isolated Limb Perfusion"). Therefore, a tourniquet on the skin provided external pressure.

12. Claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 38-42 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,627,616. Although the conflicting claims are not identical, they are not patentably distinct from each other because occluding the blood vessel as claimed in the instant invention is how the pressure was increased in the method of claim 1 in '616. Naked DNA in claim 1 of '616 is in claim 2 of the instant application. The species of delivering to skeletal muscle cells in the instant application is encompassed by "extravascular cells" in claim 1 of '616 and could have been specifically claimed. The species of inserting papaverine in claim 3 of '616 is a species of administering immunosuppressive treatment as in claim 1 of the instant application. Injecting a blood vessel in a limb as in claim 1 of the instant application is a species of injecting a blood vessel lumen *in vivo* as in claim 1 of '616.

Conclusion

No claim is allowed.

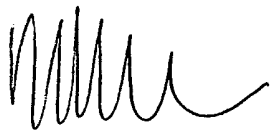
Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER